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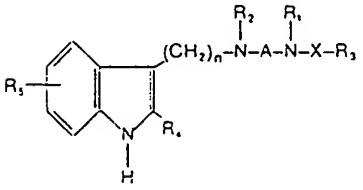
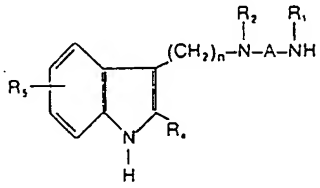
(54) New indole derivatives, processes for their preparation, and pharmaceutical compositions containing them.

(57) Indole compounds useful for the treatment of hypertension, of formula



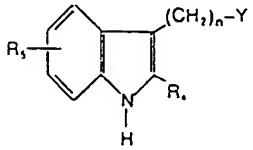
wherein n is 2 or 3, A is 1,4-cyclohexylidene or trimethylene and R_1 is H or alkyl, or A together with NR_1 is 4-piperidyl, R_2 is hydrogen or alkyl, R_3 is alkyl, cycloalkyl, amino, alkylamino, dialkylamino, phenylamino, unsubstituted or substituted phenyl or benzyl, pyridylmethyl or an heterocycle, R_4 is hydrogen, chlorine, bromine or alkyl, R_5 is hydrogen, alkyl, alkoxy or alkylthio, and X is –CO– or –CS, a process for their production which comprises

a) acylating a compound of formula II

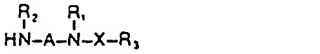


wherein n, A and R_1 to R_5 are as defined above, or

b) condensing a compound of formula III



wherein n, R_4 and R_5 are as defined above, and Y is a leaving group, with a compound of formula IV



wherein A, R_1 to R_3 and X are as defined above.

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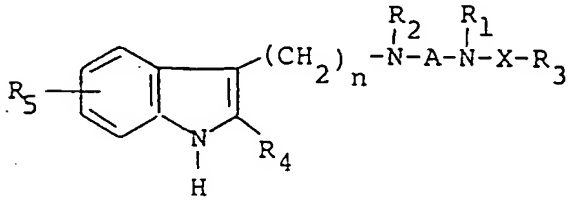
NEW INDOLE DERIVATIVES, PROCESSES FOR THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to new indole derivates, processes for their preparation, and pharmaceutical compositions containing them.

In accordance with the invention there are provided new compounds of formula I



(I)

wherein n is 2 or 3,

either A is trimethylene optionally substituted by (C_{1-4}) alkyl or 1,4-cyclohexylidene and

R_1 is hydrogen or (C_{1-5}) alkyl,

or A together with R_1 and the nitrogen atom to which R_1 is bound, form a 4-piperidyl radical,

R_2 is hydrogen or (C_{1-5}) alkyl,

R_3 is (C_{1-4}) alkyl; (C_{3-6})cycloalkyl; amino; (C_{1-4})alkylamino; di(C_{1-4})alkylamino; phenylamino wherein the phenyl ring is

unsubstituted or mono-, di- or trisubstituted independently by halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy or di(C_{1-4})alkylamino; phenyl or benzyl wherein the phenyl rings are unsubstituted or mono-, di- or trisubstituted independently by halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy or di-(C_{1-4})alkylamino; 2-, 3- or 4-pyridylmethyl; or an aromatic 5- or 6-membered heterocycle containing one heteroatom chosen from nitrogen, oxygen or sulphur and optionally additional one or two nitrogen atoms,

R_4 is hydrogen, chlorine, bromine or (C_{1-4})alkyl,

R_5 is hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy or (C_{1-4})alkylthio,

and X is -CO- or -CS-.

Any alkyl, alkoxy or alkylthio radical contains preferably two carbon atoms, especially one carbon atom. Halogen means fluorine, chlorine, bromine or iodine, especially chlorine.

When A is 1,4-cyclohexylidene, this may be cis or trans-1,4-cyclohexylidene.

When A is optionally substituted trimethylene, this is preferably either unsubstituted or mono-substituted, conveniently at the middle carbon atom.

When R_1 and R_2 are chosen from hydrogen or alkyl, these are preferably alkyl.

Conveniently A is optionally substituted trimethylene or 1,4-cyclohexylidene. Preferably A is optionally substituted trimethylene.

When R_3 is or contains a dialkylamino radical, the alkyl groups are preferably the same. When R_3 is an optionally substituted phenyl or phenylamino radical, the substituents are conveniently identical. Conveniently these radicals are unsubstituted or monosubstituted preferably in the para position. When R_3 is a heterocycle, conveniently this contains one heteroatom chosen from nitrogen, oxygen or sulphur and optionally a second nitrogen atom, e.g. thienyl, furyl, pyrrolyl, pyridyl or pyrazinyl. Conveniently the heterocycle is bound to X by a ring carbon atom adjacent to a heteroatom.

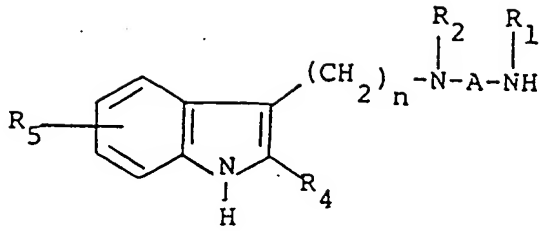
R_3 is preferably unsubstituted phenyl.

R_4 and R_5 are conveniently hydrogen.

X is conveniently -CO-.

The present invention provides a process for the production of a compound of formula I as defined above, which comprises

a) acylating a compound of formula II

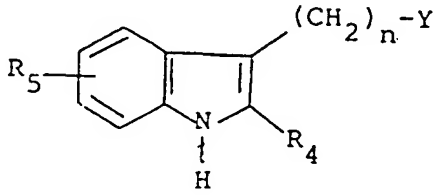


(II)

wherein n, A and R_1 to R_5 are as defined above,

or

b) condensing a compound of formula III

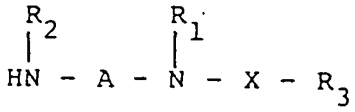


(III)

wherein n, R_4 and R_5 are as defined above,

and Y is a leaving group,

with a compound of formula IV



(IV)

wherein A, R_1 to R_3 and X are as defined above.

Process a) may be effected in conventional manner for the production of amides or thio-amides from amines. For example there may be used, as acylating agent, a compound of formula V

(V)

wherein X is as defined above, R_3' has the same signification as R_3 but is other than amino, alkyl-

amino and optionally substituted phenylamino and Z is chlorine or bromine. The reaction may be effected conveniently in a solvent such as pyridine and at temperatures from 0 to 25°. Alternatively when R_3 is amino, alkylamino or optionally substituted phenylamino, there may be used a compound of formula VI

$$X = R_6 \qquad \text{(VI)}$$

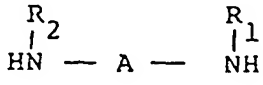
wherein X is as defined above and R_6 is imino, alkylimino or optionally substituted phenylimino. The reaction may be effected conveniently in a solvent such as dimethylformamide and at temperatures from 5 to 25°. A compound of formula VI wherein R_6 is imino may be prepared in situ from potassium or sodium cyanate or thiocyanate, by treatment with acid , for example hydrochloric acid.

Process b) may be effected in conventional manner for a condensation reaction to produce a secondary or tertiary amine. Y is conveniently chlorine, bromine, iodine, tosyloxy or mesyloxy. The reaction may be conveniently effected in acetone or dimethylformamide. Suitable reaction temperatures are from 20 to 150°.

The compounds of formula I may be isolated from the reaction mixture and purified in known

manner. The free base forms may be converted into acid addition salt forms in the usual manner and vice versa. Suitable acids for salt formation are hydrochloric acid, oxalic acid, fumaric acid naphthalene-2-sulphonic acid and naphthalene-1,5-disulphonic acid.

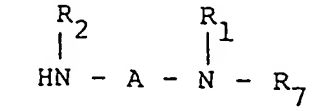
The starting material of formula II may be produced from a compound of formula III and a compound of formula VII



(VII)

wherein A, R_1 and R_2 are as defined above, in analogous manner to process b).

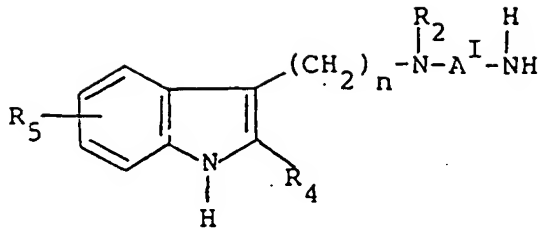
When the amine of formula VII is unsymmetrical, the conditions should be chosen to avoid the formation of the undesired corresponding compound produced by condensation at the nitrogen atom bearing the R_1 substituent. For this purpose the amine may be used in protected form of formula VIII



(VIII)

wherein R_7 is a protecting group, such as benzyl or benzyloxy, which may be removed from the resulting product, e.g. by hydrogenolysis.

A starting material of formula IIa



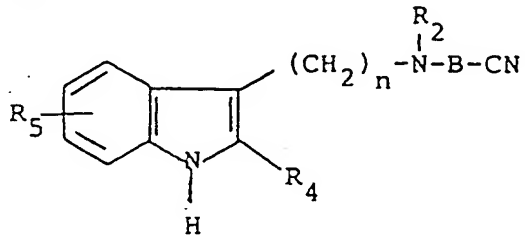
(IIa)

wherein A^I is $-CH(R_8)-CH_2-CH_2-$ or

$-CH_2-CH(R_8)-CH_2-$ and wherein R_8 is (C_{1-4})alkyl and

n, R_2, R_4 and R_5 are as defined above,

may alternatively be produced by reducing a compound of formula IX



(IX)

wherein B is $-CH(R_8)-CH_2-$ or $-CH_2-CH(R_8)-$

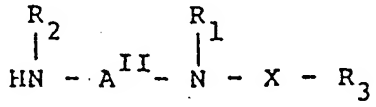
and n, R_2, R_4, R_5 and R_8 are as defined above, e.g. by hydrogenation in the presence of Raney-nickel.

Any starting material of formula II wherein R_1 and/or R_2 is hydrogen may be converted into a corresponding compound wherein R_1 and R_2 are both alkyl, or R_1 is alkyl and R_2 is hydrogen under appropriate selective alkylation conditions.

The starting material of formula IV may be produced by acylating an amine of formula VII in

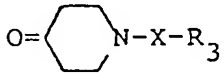
analogous manner to process a). If desired, one nitrogen atom of an unsymmetrical amine may be protected to facilitate production of the desired product.

A starting material of formula IVa



(IVa)

wherein X, R_2 and R_3 are as defined above and A^{II} together with R_1 and the nitrogen atom to which R_1 is bound, form a 4-piperidyl radical, may alternatively be produced by acylating 4-piperidone with a compound of formula V or VI and condensing the resulting compound of formula X



(X)

wherein X and R_3 are as defined above, with a compound of formula XI

$$R_2\text{-}NH_2 \qquad \text{(XI)}$$

wherein R_2 is as defined above, under simultaneous reduction, e.g. with hydrogen in presence of a catalyst.

Insofar as the production of any starting material is not particularly described, these are known or may be produced in conventional manner or in a manner analogous to that described above.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade.

EXAMPLE 1 N-benzoyl-N'-[3-(3-indolyl) propyl]-N'-methyl-1,3-diaminopropane

A solution of 10.1 g benzoyl chloride in 15 ml anhydrous methylene chloride is added dropwise with stirring for 25 minutes between 0 and 10° to a solution of 14.5 g N-[3-(3-indolyl)propyl]-N-methyl-1,3-diaminopropane in 150 ml anhydrous pyridine and the reddish clear solution is stirred for 2 hours at 0°. The reaction mixture is divided between a 2N sodium carbonate solution and methylene chloride, and the organic phase is washed, dried and evaporated. Chromatographic purification of the resinous product on aluminium oxide using methylene chloride with 0.1 to 0.3% of methanol yields the title coumpound. The naphthalene-2-sulfonate-dihydrate, obtained by conventional methods, melts at 73-74° after crystallization from methanol/water/ethyl acetate (1:1:1) .

The starting material may be obtained as follows :

a) A mixture of 57 g trifluoroacetic acid and 105 g trifluoroacetic anhydride in 400 ml anhydrous acetonitrile are added dropwise to a stirred suspension of 95.1 g 3-(3-indolyl)propionic acid in 500 ml anhydrous acetonitrile and maintained with stirring at -15° for 30 minutes.

Under good cooling 500 ml anhydrous pyridine are added between -20 and -15° and quickly 238 ml of a 4.2 N solution of anhydrous methylamine in acetonitrile. The mixture is warmed with stirring at 0° for 15 minutes and maintained to 0° for 3 hours. 3-(3-indolyl)-N-methyl-propionamide (M.pt 97-98° after crystallization from methylene chloride/ethyl acetate) is obtained after working up.

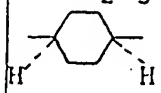
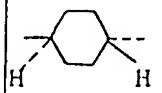
b) A solution of 60.6 g 3-(3-indolyl)-N-methyl-propionamide in 500 ml anhydrous tetrahydrofuran are added dropwise at 25° for 15 minutes under nitrogen atmosphere to a suspension of 34.2 g lithium aluminium hydride in 800 ml anhydrous tetrahydrofuran and maintained at 66° for 3 hours. N-methyl-3-(3-indolyl)-propylamine (M.pt 81-82° after crystallization from methylene chloride/ethyl acetate) is obtained after working up.

c) A mixture of 37.6 g N-methyl-3-(3-indolyl)-propylamine and 21.2 g acrylonitrile in 65 ml anhydrous 1,2-dimethoxyethane are warmed with stirring at 60° for $2\,^{1}/_{2}$ hours. N-(2-cyanoethyl)-N-methyl-3-(3-indolyl)propylamine (M.pt 48-49° after crystallization from isopropyl ether) is obtained after working up.

d) 36.2 g N-(2-cyanoethyl)-N-methyl-3-(3-indolyl)propyl

amine are hydrogenated at normal pressure and at room temperature with 20 g Raney-nickel catalyst in 400 ml dioxan and 400 ml of a 10% ammonia solution. N-[3-(3-indolyl)propyl]-N-methyl-1,3-diaminopropane is obtained after working up. M.pt of the neutral fumarate: 180-181° (with decomposition) after crystallization from ethanol.

From the appropriate compounds of formula II the following compounds of formula I wherein X is -CO- may be obtained in analogous manner to Example 1.

Ex.	n	R_1	A	R_2	R_3	R_4	R_5	M.Pt.
a)	2	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	H	122-24° 1) 10)
b)	2	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	4-OC_2H_5	189-190° 9) 10)
c)	3	H	$-(CH_2)_3-$	$-CH_3$	phenyl	$-CH_3$	H	
d)	3	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	6-SCH_3	
e)	3	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	5-OCH_3	
f)	3	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	4-OCH_3	
g)	3	H	$-(CH_2)_3-$	$-C_2H_5$	phenyl	H	H	amorphous 6)
h)	3	$-CH_3$	$-(CH_2)_3-$	$-CH_3$	phenyl	H	H	124-126° 1)
i)	3	$-n-C_3H_7$	$-(CH_2)_3-$	$-CH_3$	phenyl	H	H	82-84° 1) 7)
j)	3	H	$-(CH_2)_3-$	$-CH_3$	benzyl	H	H	amorphous 8)
k)	2	H		$-CH_3$	phenyl	H	H	173-175° 2) 10)
l)	2	H		$-CH_3$	phenyl	H	H	133-134°
m)	3	H	$-(CH_2)_3-$	$-CH_3$	3,4,5-trimethoxybenzyl	H	H	77-80° 2)
n)	3	H	$-(CH_2)_3-$	$-CH_3$	o-chlorophenyl	H	H	amorphous 6)

Ex.	n	R_1	A	R_2	R_3	R_4	R_5	M.Pt.
o)	2	H	$-(CH_2)_3-$	H	diethylamino	H	H	191-192° 3)
p)	2	H	$-(CH_2)_3-$	$-CH_3$	dimethylamino	H	H	85-87°
q)	2	H	$-(CH_2)_3-$	$-CH_3$	p-methoxyphenyl	H	H	133-135° 2) 10)
r)	3	H	$-(CH_2)_3-$	$-CH_3$	p-dimethylamino-phenyl	H	H	107-108°
s)	3	H	$-(CH_2)_3-$	$-CH_3$	m-tolyl	H	H	amorphous 6)
t)	2	H	$-(CH_2)_3-$	$-n-C_3H_7$	p-tolyl	H	H	181-183° 2) 10)
u)	3	H	$-(CH_2)_3-$	$-CH_3$	m-chlorophenyl	H	H	133-134° 1)
v)	2	H	$-(CH_2)_3-$	$-CH_3$	p-chlorophenyl	H	H	161-163° 2) 10)
w)	3	H	$-(CH_2)_3-$	$-CH_3$	3,5-dimethoxy-phenyl	H	H	137-138° 2) 10)
x)	3	H	$-(CH_2)_3-$	$-CH_3$	3,4,5-trimethoxy-phenyl	H	H	103-105° 2) 10)
y)	3	H	$-(CH_2)_3-$	$-CH_3$	o-methoxyphenyl	H	H	amorphous 6)
z)	2	H	$-(CH_2)_3-$	$-CH_3$	2-furyl	H	H	95-96°
aa)	3	H	$-(CH_2)_3-$	$-CH_3$	2-furyl	H	H	80-82° 1)
ab)	3	H	$-(CH_2)_3-$	$-CH_3$	2-thienyl	H	H	82-84° 1) 7)

Ex.	n	R_1	A	R_2	R_3	R_4	R_5	M.Pt.
ac)	3	H	$-(CH_2)_3-$	$-CH_3$	2-pyridyl	H	H	122-124° 5) 10)
ad)	3	H	$-(CH_2)_3-$	$-CH_3$	3-pyridyl	H	H	
ae)	3	H	$-(CH_2)_3-$	$-CH_3$	4-pyridyl	H	H	118-121° 4) 10)
af)	3	H	$-(CH_2)_3-$	$-CH_3$	pyrazinyl	H	H	174-175° 9) 10)
ag)	3	H	$-(CH_2)_3-$	$-CH_3$	2-pyridylmethyl	H	H	amorphous
ah)	3	H	$-(CH_2)_3-$	$-CH_3$	2-pyrrolyl	H	H	89-91° 1) 7)
ai)	2	$-CH_3$	$-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2-$	$-CH_3$	phenyl	H	H	114-115° 11)
aj)	2	H	$-(CH_2)_3-$	$-CH_3$	4-hydroxyphenyl	H	H	
ak)	3	H	$-(CH_2)_3-$	$-CH_3$	4-hydroxyphenyl	H	H	
al)	3	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	6-CH_3	

Ex.	n	R_1	A	R_2	R_3	R_4	R_5	M.Pt.
am)	3	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	5-CH_3	148-149° 9)10)
an)	3	H	$-(CH_2)_3-$	$-CH_3$	phenyl	H	4-CH_3	
ao)	3	H	$-(CH_2)_3-$	$-C_2H_5$	phenyl	H	H	

1) naphthalene -2-sulfonate
2) hydrogen oxalate
3) bis[base]naphthalene-1,5-disulfonate
4) dihydrobromide
5) dihydrochloride 1/2 H_2O
6) dihydrogen phosphate
7) monohydrate
8) bis[base]sulphate
9) bis[base]fumarate
10) with decomposition
11) hydrogen fumarate

EXAMPLE 2: N-phenylcarbamoyl-N'-[2-(3-indolyl)ethyl]-N'-methyl-1,3-diaminopropane

3 ml phenyl isocyanate are added dropwise between 5 and 10° and with stirring to a solution of 5.8 g N-[2-(3-indolyl)ethyl]-N-methyl-1,3-diaminopropane in 25 ml anhydrous dimethylformamide. The solution is stirred for an hour between 10 and 15° and evaporated. The residue is dried in high vacuum and chromatographied on silicagel using methylene chloridewith 6 to 10% methanol, to yield the title compound (M.pt. of the hydrogen maleate 153-155° with decomposition after crystallization from alcohol/acetone).

The starting material may be obtained as follows:

a) Reaction of 3-[2-methylamino)ethyl]indole with acrylonitrile in dimethoxy-ethane yields the N-(2-cyanoethyl)-N-methyl-2-(3-indolyl)ethylamine which is worked up further directly.

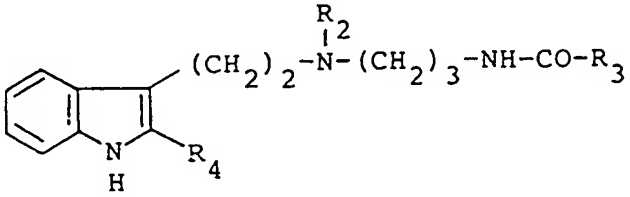
b) Reduction of N-(2-cyanoethyl)-N-methyl-2-(3-indolyl)-ethylamine with Raney-Nickel catalyst yields the N-[2-(3-indolyl)ethyl]-N-methyl-1,3-diaminopropane (M.pt. of the fumarate 153-154°).

EXAMPLE 3: N-Benzoyl-N'-[2-(3-indolyl)ethyl]-1,3-diaminopropane

A solution of 8 g N-benzoyl-1,3-diaminopropane, 6,7 g 3-(2-bromoethyl)indole and 5 ml anhydrous triethylamine in 15 ml anhydrous dimethylformamide is maintained for 72 hours

in nitrogen atmosphere. A dilute ammonia solution and methylene chloride are then added to the reaction mixture and the organic phase is dried and evaporated. The residue is chromatographied on silicagel using as eluant methylene chloride+ 5% methanol + 0.3% ammonia, to yield the title compound (M.pt. of the naphthalene-2-sulfonate 203-204° with decomposition after crystallization from ethanol).

The following compounds of formula



may be obtained in analogous manner to Example 3 :

Table

Ex. No.	R_2	R_3	R_4	M.Pt.
a)	$-n-C_3H_7$	p-tolyl	H	181-183° 1) 3)
b)	$-CH_3$	p-methoxyphenyl	H	133-135° 1) 3)
c)	$-CH_3$	p-chlorophenyl	H	161-163° 1) 3)
d)	$-CH_3$	phenyl	H	122-124° 2) 3)
e)	$-CH_3$	2-furyl	H	95-96°
f)	$-CH_3$	phenyl	Br	148-150° 1) 3)

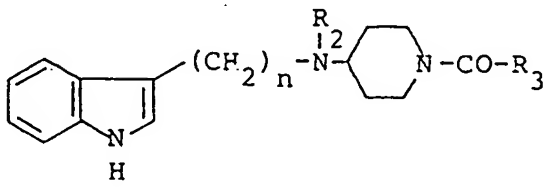
1) hydrogen oxalate

2) naphthalene-2-sulfonate

3) with decomposition

EXEMPLE 4:

From the appropriate 4-amino-piperidines and 2-(3-indolyl)ethyl bromide or 3-(3-indolyl)propyl bromide, the following compounds of formula



may be obtained in analogous manner to Example 3:

Table

Ex. No.	n	R_2	R_3	M.Pt.
a)	2	$-CH_3$	phenyl	131-133° 3)
b)	3	$-CH_3$	phenyl	201-203° 1) 3)
c)	2	iso-C_4H_9	phenyl	152-154° 2) 3)
d)	2	H	phenyl	151-152° 3)
e)	2	$-CH_3$	phenylamino	58-60°
f)	2	H	dimethylamino	119-120°

1) naphthalene-2-sulfonate

2) hydrochloride

3) with decomposition

The compounds of formula I exhibit pharmacological activity in animals. In particular, the compounds exhibit anti-hypertensive activity, as indicated by

standard tests, e.g. in the awake renal hypertonic Grollman rat upon administration of 1 to 50 mg/kg animal body weight of the compounds, and in the awake renal hypertonic Goldblatt dog upon administration of 1 to 10 mg/kg animal body weight of the compounds.

The compounds are therefore indicated for use as anti-hypertensives. For this use an indicated daily dose is from about 10 to about 2000 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 2,5 to about 1000 mg, or in sustained release form.

A particularly interesting compound is the Example 1 compound.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such salts exhibit the same order of activity as the free base forms.

The invention also provides a pharmaceutical composition comprising a compound of formula I, in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. A suitable pharmaceutical form is a capsule.

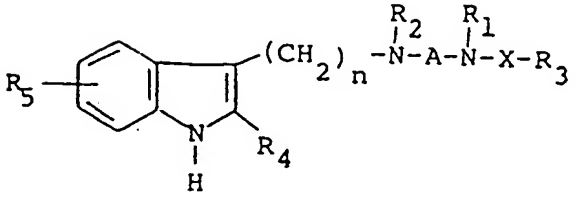
In one group of compounds n is 3, A is trimethylene, R_1 is hydrogen or (C_{1-5})alkyl, R_2 is hydrogen or (C_{1-5})alkyl, R_3 is phenyl or benzyl unsubstituted or mono-, di- or trisubstituted independently by

halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy or di-(C_{1-4})alkylamino; (C_{3-6})cycloalkyl; or an aromatic 5- or 6-membered heterocycle containing one heteroatom chosen from nitrogen, oxygen or sulphur, R_4 is hydrogen, chlorine, bromine or (C_{1-4})alkyl, R_5 is hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, or (C_{1-4})alkylthio, and X is -CO-.

In another group of compounds n is 2, either A is trimethylene and R_1 is hydrogen or (C_{1-5}) alkyl, or A together with R_1 and the nitrogen atom to which R_1 is bound form a 4-piperidyl radical, and R_2 is hydrogen or (C_{1-5})alkyl, R_3 is (C_{1-4})alkyl; phenyl unsubstituted or mono-, di- or trisubstituted independently by halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy; (C_{3-6})cycloalkyl; or an aromatic 5- or 6-membered heterocycle containing one heteroatom chosen from nitrogen, oxygen or sulphur, R_4 is hydrogen, chlorine, bromine or (C_{1-4})alkyl, R_5 is hydrogen, (C_{1-4})alkyl or (C_{1-4})alkoxy, and X is -CO- or -CS.

WHAT WE CLAIM IS :

1) A compound of formula I



(I)

wherein n is 2 or 3,

either A is trimethylene optionally substituted by (C_{1-4})alkyl or 1,4-cyclohexylidene and R_1 is hydrogen or (C_{1-5}) alkyl,

or A together with R_1 and the nitrogen atom to which R_1 is bound, form a 4-piperidyl radical,

R_2 is hydrogen or (C_{1-5})alkyl,

R_3 is (C_{1-4}) alkyl; (C_{3-6})cycloalkyl; amino; (C_{1-4})alkylamino; di(C_{1-4})alkylamino; phenylamino wherein the phenyl ring is unsubstituted or mono-, di- or trisubstituted independently by halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy or di(C_{1-4})alkylamino; phenyl or benzyl wherein the phenyl rings are unsubstituted or mono-, di- or trisubstituted independently by halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy or di-(C_{1-4})alkylamino; 2-, 3- or 4-pyridylmethyl; or an aromatic 5- or 6-membered heterocycle containing one heteroatom chosen from nitrogen, oxygen or sul-

phur and optionally additional one or two nitrogen atoms,

R_4 is hydrogen, chlorine, bromine or (C_{1-4})alkyl,

R_5 is hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy or (C_{1-4})alkylthio,

and X is -CO- or -CS-.

2) A compound of claim 1

wherein n is 3,

A is trimethylene,

R_1 is hydrogen or (C_{1-5})alkyl,

R_2 is hydrogen or (C_{1-5})alkyl,

R_3 is phenyl or benzyl unsubstituted or mono-, di- or trisubstituted independently by halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy or di-(C_{1-4})alkylamino; (C_{3-6})cycloalkyl; or an aromatic 5- or 6-membered heterocycle containing one heteroatom chosen from nitrogen, oxygen or sulphur,

R_4 is hydrogen, chlorine, bromine or (C_{1-4})alkyl,

R_5 is hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, or (C_{1-4}) alkylthio,

and X is -CO-.

3) A compound of claim 1

wherein n is 2

either A is trimethylene and R_1 is hydrogen or (C_{1-5}) alkyl,

or A together with R_1 and the nitrogen atom to

which R_1 is bound form a 4-piperidyl radical,

R_2 is hydrogen or (C_{1-5})alkyl,

R_3 is (C_{1-4})alkyl; phenyl unsubstituted or mono-, di- or trisubstituted independently by halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy; (C_{3-6})cycloalkyl; or an aromatic 5- or 6-membered heterocycle containing one heteroatom chosen from nitrogen, oxygen or sulphur

R_4 is hydrogen, chlorine, bromine or (C_{1-4})alkyl,

R_5 is hydrogen, (C_{1-4})alkyl or (C_{1-4})alkoxy,

and X is -CO- or -CS- .

4) A compound of claim 1 which is N-benzoyl-N'-[3-(3-indolyl)propyl]-N'-methyl-1,3-diaminopropane.

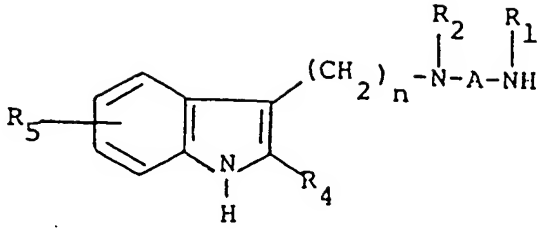
5) A compound of claim 1 which is N-methyl-N-benzoyl-N'-methyl-N'-[2-(3-indolyl)ethyl]-2-methyl-1,3-diaminopropane.

6) A compound of any one of claims 1 to 5 in free base form.

7) A compound of any one of claims 1 to 5 in acid addition salt form.

8) A process for the production of a compound of formula I as defined in claim 1, which comprises

a) acylating a compound of formula II

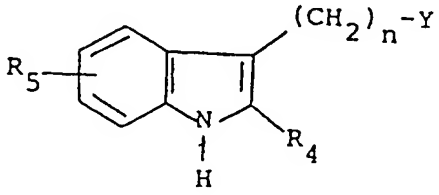


(II)

wherein n, A and R_1 to R_5 are as defined in claim 1,

or

b) condensing a compound of formula III

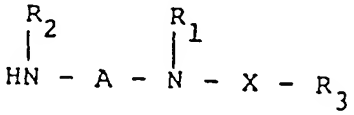


(III)

wherein n, R_4 and R_5 are as defined in claim 1,

and Y is a leaving group,

with a compound of formula IV



(IV)

wherein A, R_1 to R_3 and X are as defined in claim 1.

9) A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

European Patent Office

EUROPEAN SEARCH REPORT

0000355
Application number
EP 78 10 0274

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	CHEMICAL ABSTRACT (1974) vol. 81, 105181k & Khim- Farm. Zk. 1974 8(6)-7-11. * Abstract *	1,2,3, 9

CLASSIFICATION OF THE APPLICATION (Int. Cl.²)

C 07 D 209/14
C 07 D 209/16
C 07 D 209/30
C 07 D 401/12
// C 07 D 209/18

TECHNICAL FIELDS SEARCHED (Int.Cl.²)

C 07 D 209/14
C 07 D 209/16
C 07 D 209/30
C 07 D 401/12

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	26-10-1978	MAISONNEUVE

EPO Form 1503.1 06.78

(65)

(19) Europäisches Patentamt
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(11) Publication number: **0 000 355**
A1

(12) # EUROPEAN PATENT APPLICATION

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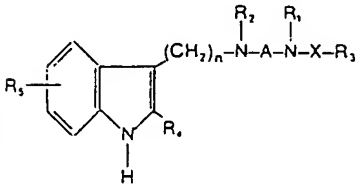
No	références, formules, pages à photocopier, etc	No	classement
1	Complete specification see ex 1, c-j, m, n, r, s, w-y, aa-ah, ak-ao	1	C07D 209/14
2	p 9, 9, 10 ex 1a	2	~~C07D 209/18~~
3	Complete specification see ex 1 ab, kl, o-q, t, v, z, ai, aj 2, 3	3	C07D 209/16
4	p 9, 18 + claims see ex 4	4	124 HCl 86 M + 823
			BERLIN: C07D 401/12

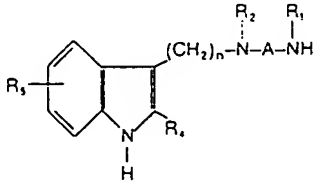
(54) New indole derivatives, processes for their preparation, and pharmaceutical compositions containing them.

(57) Indole compounds useful for the treatment of hypertension, of formula



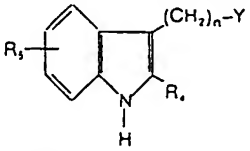
wherein n is 2 or 3, A is 1,4-cyclohexylidene or trimethylene and R_1 is H or alkyl, or A together with NR. is 4-piperidyl, R_2 is hydrogen or alkyl, R_3 is alkyl, cycloalkyl, amino, alkylamino, dialkylamino, phenylamino, unsubstituted or substituted phenyl or benzyl, pyridylmethyl or an heterocycle, R_4 is hydrogen, chlorine, bromine or alkyl, R_5 is hydrogen, alkyl, alkoxy or alkylthio, and X is –CO– or –CS, a process for their production which comprises

a) acylating a compound of formula II

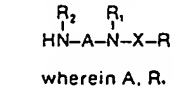


wherein n, A and R_1 to R_5 are as defined above, or

b) condensing a compound of formula III



wherein n, R_4 and R_5 are as defined above, and Y is a leaving group, with a compound of formula IV



wherein A, R_1 to R_3 and X are as defined above.

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